



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁴ : A61K 47/00, 9/14, 9/16		A1	(11) International Publication Number: WO 88/06893 (43) International Publication Date: 22 September 1988 (22.09.88)
(21) International Application Number: PCT/DK88/00044 (22) International Filing Date: 11 March 1988 (11.03.88) (31) Priority Application Number: 1302/87 (32) Priority Date: 13 March 1987 (13.03.87) (33) Priority Country: DK		(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent). Published <i>With international search report.</i>	
(71) Applicant: BENZON PHARMA A/S [DK/DK]; Halm-torvet 29, DK-1700 Copenhagen V (DK). (72) Inventor: IBSEN, Lars, Skov ; Franckesvej 6, 4 th., DK-2000 Frederiksberg C (DK). (74) Agent: PLOUGMANN & VINGTOFT; Sankt Annæ Plads 11, DK-1250 Copenhagen K (DK).			
(54) Title: AN ORAL COMPOSITION CONTAINING PARTICLES COMPRISING AN ACTIVE SUBSTANCE (57) Abstract <p>An oral composition which is adapted to be dispersed in an aqueous carrier substantially immediately prior to administration comprises a multiplicity of particles comprising an active substance, the particles being combined with one or more gelling or swelling agents capable of forming a viscous medium around the particles in an aqueous carrier as well as being provided with a masking surface layer when dispersed in the aqueous carrier. This serves to mask uneven surfaces on the particles and prevent them from adhering to oral mucosa when the composition is ingested and thus makes it easier to administer large dosages of an active substance. The masking surface layer is preferably provided by an increased viscosity of the viscous medium in the immediate vicinity of the particles relative to the viscosity of the surrounding aqueous carrier. A ready-to-use composition is prepared by mixing the composition with an aqueous carrier substantially immediately prior to administration of the composition.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT Austria	FR France	ML Mali
AU Australia	GA Gabon	MR Mauritania
BB Barbados	GB United Kingdom	MW Malawi
BE Belgium	HU Hungary	NL Netherlands
BG Bulgaria	IT Italy	NO Norway
BJ Benin	JP Japan	RO Romania
BR Brazil	KP Democratic People's Republic of Korea	SD Sudan
CF Central African Republic	KR Republic of Korea	SE Sweden
CG Congo	LI Liechtenstein	SN Senegal
CH Switzerland	LK Sri Lanka	SU Soviet Union
CM Cameroon	LU Luxembourg	TD Chad
DE Germany, Federal Republic of	MC Monaco	TG Togo
DK Denmark	MG Madagascar	US United States of America
FI Finland		

r the pre-mixed gel. This may in some cases present the important advantage over the known premanufactured suspensions that the composition of the present invention has an increased storage stability and permits a wider range of active substances to be incorporated therein, as most active substances at present contemplated to be administrable in these compositions are in fact unstable in the presence of an aqueous carrier or become unstable within a relatively short period of time. The composition of the invention also shows improved packaging, handling and transportation properties due to the fact that the ready-to-use suspension is prepared *in situ* either by the end user or by medical staff. Furthermore, it is easy to measure out exact dosages (reproducible amounts of) of the active substance in the composition of the invention, because the particles comprising the active substance are present in the composition in dry form (which is easier to measure out), or optionally in unit dosage form, until substantially immediately prior to administration (i.e. from about a few seconds to about an hour), the particles comprising substantially uniform amounts of active substance, whereas exact dosages of the active substance are difficult to obtain from ready-made suspensions since there is no homogeneous admixture of the active substance in the ready-made suspensions and since precise dosages are difficult to measure out for both patients and nursing staff.

The compositions of the invention make it possible to administer large individual dosages of an active substance in that they do not impose the limitations with respect to size imposed by conventional tablets or capsules. Consequently, the compositions of the inventions are particularly well suited for administration of active substances which are generally administered in large dosages. Furthermore, according to the invention, the masking surface layer formed on the particles when the composition is made ready for use provides the particles with a smooth surface which serves to mask uneven surfaces on the particles comprising the active substance and prevent them from adhering to oral mucosa, or to containers where the ready-to-use compositions are prepared, and may also contribute to masking any unpleasant taste of the active substance. The composition of the present invention is hereby distinguished from the ready-to-use

product disclosed in FR 2 473 307 which comprises powdered di-hydroxybutylether to be dispersed in a gelling agent. In this dispersion, a slurry is formed of dihydroxybutyl ether particles in a viscous medium of the gelling agent. This medium has a uniform viscosity throughout the dispersion and hence does not show the advantageous feature of forming a smooth surface layer substantially around each particle of the active substance. The particles of the active substance may therefore be expected to separate from the viscous medium and either sediment in the container in which the dispersion is made, after standing for a certain period of time, or adhere to its walls or to oral mucosa when the product is ingested. It has also been found that these dispersions require a disproportionately large amount of liquid relative to the amount of active substance in order to obtain an adequate dispersion of the gelling agent, whereas the compositions of the present invention may include any desired amount of active substance without necessitating a corresponding increase in the amount of liquid required to prepare the ready-to-use composition.

20

DETAILED DISCLOSURE OF THE INVENTION

It is contemplated that the masking surface layer on the particles may be provided by for instance a substance which will produce a foam around the particles on dispersion thereof in the aqueous carrier. However, in a currently preferred embodiment of the present invention, the masking surface layer on the particles containing the active substance is provided by an increased viscosity of the viscous medium in the immediate vicinity of the particles relative to the viscosity of the surrounding aqueous carrier. In other words, according to this embodiment, the viscous medium forms a layer of a gelled mass with a higher viscosity than the rest of the viscous medium, this gelled mass surrounding the particles, and substantially each particle, of the composition.

35 In accordance with the principles of the present invention, the gelling or swelling agent is a vital component of the present composition. Gelling agents are usually substances which form colloidal

dispersions in an aqueous environment, the colloidal particles forming a threedimensional network or grid-like structure throughout the liquid phase. In the present context, the term "gelling agent" includes sols and solid-in-liquid suspensions. It should be noted that the term "gelling or swelling agent" is also intended to include the viscous medium (gel) formed by the agent when it is dispersed in the aqueous carrier (which may be any suitable liquid such as water, juice or milk).

10 Although the viscosity of the composition on dispersion in the aqueous carrier is not particularly critical, the gelling or swelling agent should be present in a concentration which, on the one hand, is sufficient to impart a viscosity to the viscous medium surrounding the particles which is adequate to mask their gritty feel, but which, on the other hand should not be so high that it will result in a viscosity which might create difficulties when the composition dispersed in the aqueous carrier is to be emptied from the container in which it has been mixed, giving rise to undesirable dosage variations. In other words, the gelling or swelling agent should preferably not be one which forms a solid or nearly solid gel throughout the composition although as mentioned above, the viscous medium formed by the gelled substance preferably has a higher viscosity in the immediate vicinity of the particles.

25 It should be noted that although the consistency of the aqueous carrier when admixed with the gelling or swelling agent to a large extent depends on the concentration in which the gelling or swelling agent is present in the ready-to-use composition, the desired viscosity may often be obtained by adjusting the amount of gelling or swelling agent combined with the particles comprising the active substance, by selecting a gelling or swelling agent with a specific degree of polymerization, or by mixing high-viscous and low-viscous gelling or swelling agents in specific ratios to obtain the desired viscosity. An advantageous viscosity of the ready-to-use composition may be from that of a relatively thin oil to that of a relatively thick cream or paste.

Furthermore, the viscous gel medium may be one which becomes less viscous or dissolves under the conditions, especially with respect to

pH and enzymes, prevailing in the stomach so that it does not influence the release of the active substance from the particles. On the other hand, the gelling or swelling agent may advantageously be one which is stable for a sufficient period of time in a certain pH-range. Apart from this, the gelling or swelling agent should preferably be one which does not depend on heating in order to form a satisfactory gel, and should preferably be one which may be used in low concentrations to produce a desired viscosity. It should preferably be possible to regulate the properties of the gel with respect to viscosity, syneresis, etc. by external means such as adjusting the pH of the gel, or adding a reagent to the composition or the aqueous carrier to react with the gelling or swelling agent and hence influence the properties of the gel (vide the discussion below).

Examples of useful gelling or swelling agents are hydrophilic polymers selected from natural or semi-synthetic polysaccharides such as pectin, agar, dextran, carageenan, tragacanth gum, locust bean gum, acacia gum, guar gum, ghatti gum, xanthan gum, alginic acid or derivatives thereof such as sodium alginate, or a cellulose derivative, e.g. methylcellulose, carboxymethylcellulose, sodium starch glycollate, sodium carboxymethylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose and microcrystalline cellulose. Other useful gelling or swelling agents may be selected from inorganic substances such as silica and silicates (e.g. aluminium silicate, magnesium silicate, aluminium magnesium silicate and sodium silicate) and aluminium hydroxide, proteins such as gelatin or casein, and synthetic polymers such as acrylic polymers (acrylates), carboxymethylene, polyalkylene glycols, e.g. polyethylene glycol, and polyvinylpyrrolidone. Mixtures of different grades of the gelling or swelling agents may also be employed. All of these gelling or swelling agents may be dispersed in water (i.e. an aqueous carrier) and the viscosity of the gel formed by the gelling or swelling agents may be subject to control by regulating the chemical equilibria determining the concentration of reactants in the viscous medium surrounding the particles comprising the active substance. The concentration of the gelling or swelling agent will of course, in each case, depend on the desired viscosity of the ready-to-use composition, the gel-forming properties of the gelling or swelling agent.

employed, etc. However, a realistic concentration of the gelling or swelling agent for obtaining a suitable consistency of the composition is usually in the range of 0.05-20%, preferably 0.1-10%, in particular 0.2-5%, by weight of the ready-to-use composition.

- 5 In one embodiment of the composition of the invention, the particles may simply be admixed with the gelling or swelling agent in dry form. In an alternative embodiment, the particles containing the active substance and the powder or particles of the gelling or swelling agent may be kept separately: when preparing the ready-to-use composition of the invention, the gelling or swelling agent may, in this case, be dispersed in the aqueous carrier to form the viscous medium (gel) before admixture with the particles containing the active substance. It may furthermore be possible to prepare a ready-made dispersion of the gelling or swelling agent in the aqueous carrier during manufacture of the composition; this viscous gel is then kept separate from the particles comprising the active substance which are invariably stored in dry form until the composition is to be administered. It may occasionally be an advantage to prepare a ready-made dispersion of the gelling or swelling agent as some such agents are not instantly dispersed when added to an aqueous carrier, but require a certain period of time to be uniformly dispersed in the carrier and form a gel of a satisfactory viscosity. If the resulting gel has too high a viscosity to permit an easy admixture with the particles comprising the active substance, a further quantity of aqueous carrier may be added until the desired viscosity is obtained.
- 10 15 20 25

In another embodiment of the composition of the invention, the particles may be granulated together with the gelling or swelling agent. The granulation is performed by conventional means, using well-established methods, excipients, etc.

- 30 35
- In yet another embodiment of the composition of the present invention, the particles may be coated with a coating which is composed of at least one layer comprising the gelling or swelling agent. In this case, no further modification of the composition in the form of specific agents is needed in order to obtain a more highly viscous medium around the particles.

The particles may furthermore be provided with a coating layer of a film mediating controlled release of the active substance from the particle (e.g. a crystal or granule) comprising it, i.e. typically a diffusion or enteric film coating. Such a controlled-release coating
5 is usually provided when the active substance is one that acts as a local irritant on gastrointestinal mucosa, or when it is desired to obtain a prolonged effect of the active substance, in accordance with principles which are well-known to those skilled in the art. A controlled-release coating is, however, not an obligatory feature of the
10 composition of the invention. Thus, the coating may also be a water-soluble coating which serves to contain viscosity-regulating components or to mask an unpleasant taste of the active substance.

As explained above, the gelling or swelling agent serves to mask any
15 grittiness of the particles resulting from an uneven surface thereof, and to provide a slippery surface which makes the particles easier to swallow. This is particularly important when the particles comprising the active substance are above a certain size. Thus, the particles comprising the active substance typically have a size in the range of about 0.05-7 mm, for instance about 0.1-3 mm.
20

In the present context, the term "active substance" is intended to indicate not only drugs, but all kinds of substances which may play a part in biochemical processes in the body. Hence, the active substance may be selected from drugs, vitamins, micronutrients and
25 macronutrients. The composition of the invention is particularly advantageous for formulating bulky active substances since this dosage form is not limited to a specific size which is possible to swallow, contrary to what is the case with tablets or capsules. Active substances may be bulky either because large quantities of the active
30 substance are required per dosage to be administered or because the active substance itself is bulky or has to be formulated with one or more bulky excipients. Examples of bulky active substances are naproxen, ibuprofen, paracetamol, acetylsalicylic acid, potassium chloride, ampicillin, bacampicillin, cimetidine, bevantolol and ant-acids such as magnesium oxide/aluminium amino acetate, which all require dosages of 200-3000 mg per dosage, the dosages being administered up to several times a day. Other examples are vitamins (such as
35

Vitamin C), micronutrients (e.g. minerals such as Ca, Mg, Na, Fe, F, K, etc.) and combinations thereof as in conventional vitamin/mineral supplements, and macronutrients such as dietary fibres, carbohydrates (e.g. sugars) and proteins. Examples of drugs formulated with bulky excipients are drugs coupled to carriers such as cyclodextrins, antibodies, lectins, globulins, etc.

The possibility of administering large dosages of an active substance obtained by the composition of the invention has also made it feasible to combine two or more active substances in the same composition, provided that they are compatible, greatly simplifying dispensing and administration procedures in hospitals, nursing homes and other institutions where patients at present often have to ingest several tablets or capsules, each containing a different active substance, at a time. It is contemplated that the entire daily dosage of drugs and optionally other active substances may be administered once or perhaps twice a day, provided that the active substances are compatible, and one or more of the active substances may suitably be provided in controlled-release form. Such an administration regimen would both lead to improved patient compliance and lighten the work load of hospital and similar staff.

As indicated above, it is preferred to provide the masking surface layer in the form of a somewhat thicker viscous gel medium in the immediate vicinity of the particles comprising the active substance in order to mask uneven surfaces effectively. Such masking may for instance be provided by coating the particles with a gelling or swelling agent which is not easily soluble in water. Alternatively, the composition may further comprise a substance which increases the viscosity of the viscous medium formed around the particles in the aqueous carrier by the gelling or swelling agent. This viscosity-increasing substance may be included in the particles comprising the active substance. Alternatively, the viscosity-increasing substance may be included in a coating provided on the particles. The inclusion of such a viscosity-increasing agent in the composition will result in a thicker gel around the particles than in the remainder of the composition when it is admixed with the aqueous carrier, but this will nevertheless be a gel which disintegrates rather quickly after

the composition has been ing sted. Substanc s causing the medium to bec me more viscous ar und the particles may be substances which possess a specific redox potential or which form salts or chelates with the gelling or swelling agent or which increase the concentrat-
5 ion of the gelling or swelling agent or change the binding proper-
ties in the gelling or swelling agent in the immediate vicinity of
the particles.

Salt formation:

- 10 The viscosity increase in the immediate vicinity of the particles may be provided by direct salt formation by means of mono-, di- or tri-
valent ions. The ions may be both cations and anions dependent on whether the gelling or swelling agents are cationic or anionic in nature. Examples of useful cations are metal ions such as Li, Na, K,
15 Mg, Ca, Zn, Cu, Fe, Cr, Ni, Mn and Al, as well as NH₄. Combinations of these ions are also possible, e.g. Mg and Al as in aluminium magnesium silicate. Occasionally, the appropriate ion may be present in a gelling or swelling agent, e.g. Ca in calcium carboxymethylcel-
lulose, Na in sodium alginate and sodium carboxymethylcellulose, K,
20 Mg and Ca in acacia gum, NH₄, Na, K and Ca in carrageenan and Mg in magnesium silicate. Furthermore, various organic ammonium compounds such as triethanol ammoniumchloride may be employed together with carboxypolyethylene. Other ammonium ions may be formed by certain amino acids at a neutral or acid pH.
25 Examples of anions which are useful for the present purpose are Cl,
Br, SO₄, PO₄, NO₃, CO₃ and a number of organic compounds such as salts of carboxylic acids, e.g. lactic, acetic, citric, acetyl-
salicylic, benzoic, alginic, malic, stearic, palmitic, ascorbic and
30 galacturonic acid, and optionally polymerizates of acids such as amino acids, as well as carboxymethylcellulose. Apart from these, amino acids may be used, such as glutamic acid, aspartic acid, glyc-
cin, etc. Amino acids primarily form cations at a neutral or slightly acid pH, but most amino acids exist as zwitterions even under
35 slightly basic conditions.

When the local viscosity increase is obtained by means of salt for-
mation, it may be possible to regulate the rate at which the m re

highly viscous gel is formed as well as the viscosity of the resulting gel by means of the pH of the aqueous dispersion of the gelling or swelling agent in the carrier, the particle size of the salt determining the surface area accessible to the aqueous carrier, or by employing mixtures of different salts, for instance different anions of the same metal ion or different metal ions. It is, for instance, characteristic that tri-valent ions form more highly viscous gels than di-valent ions. Inclusion of such different salts in different coating layers on the particles may be employed to achieve a more specific time-dependent gel formation.

Chelate formation:

The desired viscosity increase around the particles may also be obtained by means of chelate formation. Substances useful for this purpose may be the same as those discussed above with respect to salt formation. However, a chelating agent may also increase the viscosity together with substances which are not electrically charged, or the chelating agent may in itself give rise to a viscosity increase. The mechanism of chelate formation may be utilized to regulate gel formation. Thus, EDTA (ethylenediaminetetraacetic acid) may be included in the composition of the invention to control the concentration of, for instance, metal ions (such as those listed above) in the viscous medium by chelate formation. Other chelating agents which may be employed for the same purpose may be selected from a wide range of primarily organic compounds, including various polymers such as polyoxyethylenes, peptides, proteins, polysaccharides (starch and cellulose derivatives), polyesters, etc.

Redox potential:

According to the invention, an appropriate viscosity increase around the particles may also be obtained by including substances which due to a well-defined redox potential may be used to regulate equilibria between different oxidation stages of the same substance which may have different salt or chelate forming properties. It may be possible directly to influence a gelling or swelling agent containing redox sensitive groups, e.g. easily reducible acid groups or easily oxidizable hydroxy or amine groups. Substances having useful redox

p tential include Fe, Cu, Zn, Cr, Mn and Co. Furthermore, a number f organic substances may be employed, in particular complex biological substances such as cytochromes, hemoglobins, various enzymes such as enzymes involved in the citric acid cycle or the corresponding coenzymes or prosthetic groups, in order to achieve a specific redox potential. Some of these substances may also act as gelling agents, for instance polymers such as polysaccharides which may be included in the composition of the invention in oxidized or reduced form and reduced or oxidized, respectively, in the aqueous carrier to form the viscous medium.

Local increase of gel concentration:

This may be obtained by "removing" water from the gelled gelling or swelling agent, resulting in a more highly concentrated gel. More specifically, removal of water may be achieved by applying a swelling, but water-soluble coating on the particles which coating swells in the presence of the aqueous carrier, attracting water from the surrounding gel which becomes more concentrated and hence more viscous.

Swelling agents which are useful for this purpose and which may be incorporated in a water-soluble film forming agent to form the swellable film may be substances used as conventional tablet disintegrants. Examples of such substances are starches such as corn or potato starch, cellulose derivatives such as sodium or calcium carboxymethylcellulose, methylcellulose, ethylcellulose, ethylhydroxyethylcellulose, microcrystalline cellulose, ethylmethylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, cellulose acetate phthalate, etc., other polysaccharides such as agar, alginic acid, pectin, acacia gum, tragacanth gum, xanthan gum, guar gum and ghatti gum, inorganic substances such as aluminium silicate, magnesium silicate, aluminium magnesium silicate, silica and various feldspars, proteins such as gelatin and synthetic polymers such as carboxypolymethylene and polyvinylpyrrolidone (it will be noted that these substances are in many instances identical to the ones listed above as gelling or swelling agents).

Changing the polarity of the medium:

A locally increased viscosity of the gelling or swelling agent may be obtained by including a surfactant in the composition of the invention, thus reducing the surface tension of the water in the aqueous carrier. Useful surfactants include polymers such as polyvinylpyrrolidone, polyethylene glycol and water-soluble polysaccharides, low molecular weight substances such as mono- or di-saccharides, alcohols such as ethanol and glycerol, amines such as amino acids, esters and amides such as acetylsalicylic acid and EDTA, detergents such as polysorbates, sodium lauryl sulphate and salts of fatty acids, e.g. palmitic, stearic, oleic or lauric acid, and phospholipids.

It should be noted that many of the substances mentioned above may act in different ways to increase the viscosity of the viscous medium around the particles so that it is not always possible to ascribe the viscosity increase to just one of the principles described above. In fact, the reactions which give rise to the viscosity increase are most often a combination of two or more of these principles.

If the particles are coated with a coating containing a viscosity-increasing substance, the coating may be controlled-release coating as defined above. This will make it possible to determine the release of the viscosity-increasing agent and hence the rate at which the highly viscous medium is formed by controlling the diffusion rate of the viscosity-increasing agent through the coating. Alternatively, the coating in which the viscosity-increasing agent is incorporated may be one which is independent of any intended controlled-release effect, for instance a water-soluble polymer.

Finally, the viscosity-increasing substance may be present in the aqueous carrier. In order to prevent formation of a highly viscous medium throughout the aqueous carrier, an acid, in particular a weak acid, may advantageously be present in the particles comprising the active substance or in a coating provided thereon. If so, the viscosity-increasing agent must be pH sensitive, which means that it should exert its viscosity-increasing activity in a certain pH range, its activity for instance resulting from its being soluble at a certain pH. When the acid is released from the particles or the coating

thereon, the viscosity of the medium will be incr as d in th im-
mediate vicinity of the particles. Th acid may, for instance, be
glutaminic acid, glucono delta lactone, tartaric acid, citric acid,
phosphoric acids, carbonic acids, and buffers thereof.

5 If the viscosity-increasing substance is a sparingly soluble sub-
stance and is present in the particles or in a coating on the parti-
cles, an easily dispersed substance such as a chelating agent (e.g.
sodium citrate which may be used in connection with di- or trivalent
10 metal ions used for salt formation as described above) or an affinity
chromatography or ion exchange resin may be added to the composition
in a low concentration to be present in the aqueous carrier in the
ready-to-use composition in order to provide a chemical retardation
of gel formation by the sparingly soluble viscosity-increasing sub-
stance in the particles or in a coating provided on the particles,
15 thus preventing the formation of a thick gel throughout the aqueous
carrier.

It may be an advantage to provide the composition of the invention in
a form that allows measuring out individual dosages of the active
20 substance comprised in the particles *in situ*. Thus, particles com-
prising an active substance may be dispensed according to each pa-
tient's need, i.e. each dosage may be measured according to indi-
vidual requirements, and two or more active substances may also be
mixed in this way, if required. In this embodiment of the composition
25 of the invention, particles comprising an active substance may be
stored in separate containers for each active substance, and a dosage
of each (at least one) active substance to be administered may be
measured out into another container, typically a glass, and mixed
with a measure of gelling or swelling agent in powder, tablet or pre-
30 mixed form and aqueous carrier to a satisfactory viscosity. This way
of dispensing an active substance permits greater flexibility and
individual variety in the administration of active substances.

The composition of the invention may, however, also be provided in
35 unit dosage form, typically a sachet, capsule or tablet containing a
specific amount of particles comprising one or more active substances
and opti nally also a gelling or swelling agent. This may, however
also be provided separately, either in dry f rm or as a pre-gelled

dispersion in the aqueous carrier as indicated above. The unit dosage will usually contain at least 200 mg of the active substance and often more than that as no limitations as to the maximum amount of active substance that can be incorporated in each dosage is imposed by the present formulation, contrary to conventional capsules or tablets intended for being swallowed as such. If the composition of the present invention is formulated as a capsule or tablet, it is intended to be disintegrated in an aqueous carrier such as water before ingestion. In order to facilitate dispersion of the capsule or tablet contents in the aqueous carrier, it may be an advantage to include an effervescent agent such as sodium bicarbonate; this will also accelerate the dispersion of the gelling or swelling agent in the aqueous carrier when it is present in the composition in dry form.

The composition of the invention may further comprise conventional fillers or adjuvants such as disintegrants or lubricants as well as conventional, pharmaceutically acceptable flavouring or colouring agents. The filling of capsules and sachets and the compression of tablets are performed in a manner known per se.

The invention is disclosed in further detail in the following examples which should not be construed as limiting the invention in any way.

25

30

35

MATERIALS AND METHODS

	Purified, crystalline sucrose	Supplied by Irma A/S, Denmark.
5	Paraffin	Ph. Nord. 63.
	Isopropanol	DLS (Dansk Legemiddel Standard - "Danish Drug Standard")
10	Acetyltributylcitrate	Citroflex® A4; supplied by Pfizer A/S, Denmark
	Ethylcellulose	NF XV
	Colloidal silica	USP XXI
15	Colloidal aluminium magnesium silicate	Veegum® PRO; supplied by Superfos Chemicals A/S
	Citric acid, monohydrate	Ph. Eur. Suppl. 77
20	Sodium citrate	Ph. Eur. III
	Saccharin sodium	Ph. Nord. 63 II
	Sodium chloride	Ph. Eur. I Suppl. 73, Suppl. 77.
25	Hydroxypropylmethylcellulose	Hypromellose 50 AB and Hypromellose 5 AB, USP XXI; Hypromellose 15, supplied by DAK, Denmark (in the following abbreviated to HPMC)
	Propylene glycol	Ph. Eur. III
	Polyvinylpyrrolidone	DLS 83 (in the following abbreviated to PVP)
	Purified water	Ph. Eur. 2nd Ed., 8, 1980.
35	Polyplasdone XL	crosslinked PVP; supplied by GAF A/S, Ballerup, Denmark

18

Poly thylene glycol 6000

Ph. Nrd. 63 II (in the following
abbreviated to PEG)

Dextrose

Ph. Eur. II

5 Sodium alginate

SOBALG FD 160, SOBALG FD 167 and
SOBALG FD 170; supplied by
Grindsted Products A/S, Denmark

Alginic acid

SOBALG PH 060, supplied by
Grindsted Products A/S, Denmark,

10

Potassium chloride crystals

Ph. Eur. I, size fraction 0.2-0.6
mm

Calcium hydrogen phosphate

Ph. Eur. III

15

Microcrystalline cellulose

Avicel® PH 101; DLS 83

Acetylsalicylic acid crystals

Ph. Eur. I

Antifoam emulsion

supplied by DAK, Denmark

20

Magnesium stearate

Ph. Eur. III

Talc

Ph. Eur. III

Eudragit® NE 30 D

A neutral acrylic acid ethyl ester/
methacrylic acid methyl ester-
copolymerize in the ratio 70:30,
MW >800,000, as a 30% aqueous dis-
persion, supplied by Röhm Pharma
GmbH, Darmstadt, BRD.

30

Lactose

USP XXI

Rice starch

Ph. Eur. 2nd Ed. 1985

Polysorbate 20

Ph. Eur. 2nd Ed. 1985

35

Calcium sulphate

NF XV

Titanium dioxide

Ph. Eur. 2nd Ed. 1985

Preparation of diffusion film-coated sucrose crystals

4000 g of sucrose crystals were coated with a film coating mixture composed of 53.25 g of paraffin, 18.75 g of acetyltributylcitrate, 5 350.25 g of ethyl cellulose, 5.25 g of colloidal silica and 7072.5 g of isopropanol according to the method disclosed in US Patent No. 4,572,833.

The resulting coated crystals were sieved through a 3 mm mesh sieve. 10 188 g of the crystals has a size of more than 3 mm and were discarded.

Preparation of film-coated potassium chloride crystals

150 kg of potassium chloride crystals were coated with 140 kg of an inner film coating suspension composed of 195.8 kg of purified water, 1.3 kg of HPMC 5, 0.2 kg of antifoam emulsion, 0.27 kg of magnesium stearate, 2.43 kg of talc and 86.4 kg of Eudragit® NE 30 D as well as with 15 kg of an outer film coating suspension composed of 13.5 kg of purified water, 0.75 kg of HPMC 5 and 0.75 kg of talc according to 20 the method disclosed in European Published Specification No. 153 105.

The resulting coated crystals were sieved to a size fraction of 0.425-0.71 mm.

25 EXAMPLE 1

Preparation of a pre-mixed gel and PVP-coated sucrose crystals

A pre-mixed gel was prepared from 2400 g of purified water, 125 g of Veegum® PRO, 14.1 g of citric acid, 8.5 g of sodium citrate, 2.0 g of 30 saccharin sodium and 3.0 g of sodium chloride.

The Veegum® PRO was dispersed in the water at 7000 rpm on a PIL-MIX Lab. O Uni-V homogenizer at 40-50°C for 15 min. This produced a viscous and highly thixotropic pale brown and creamy suspension. Citric acid, sodium citrate, saccharin sodium and sodium chloride were added 35 as flavouring agents. These substances were dissolved in the pre-mix d gel by further dispersi n at 8000 rpm for 2 min.

- 100 g of diffusion film-coat d sucrose crystals produced as described above were coated with a coating mixture composed of 3.0 g of HPMC 50 AB, 1.0 g of PVP, 1.0 g of propylene glycol and 100 g of purified water. The coating mixture was prepared by dissolving the HPMC 50 in the water at room temperature for about one hour on a magnetic stirrer (Struer type M 21) set at speed 8. The PVP was added and dissolved with continued stirring for about 5 min. after which propylene glycol was added. The coating mixture was then sieved through a 0.35 mm mesh sieve.
- The coating of the sucrose crystals was carried out in a fluid bed (which had been pre-heated for 10 min.) in a manner known per se, at a rate of 3.5 g of the coating mixture/min., an inlet air temperature of 40-45°C and an outlet air temperature of 32-35°C. The coated crystals were then dried for 5 min. at the same temperature and cooled. The entire coating procedure took 50 min. The resulting crystals had a white, shiny surface which under the microscope (magnification x 63) was observed to be slightly porous.
- A ready-to-use composition may be prepared by carefully mixing 2.0 g of these coated crystals with 20.58 g of the pre-mixed gel prepared above for 5-10 seconds, producing a uniform distribution of the crystals in the gel and a slightly increased viscosity which became more pronounced with further stirring. When the viscous composition was carefully placed on a flat support and rinsed with water, the viscous medium could be separated from the crystals which were found to be surrounded by the pale brown gel. It was observed under the microscope (magnification x 40) that the crystals were surrounded by a 1/2-1 mm thick highly viscous gel.
- This formulation made the crystals easy to swallow, and when a glass in which the composition had been poured was emptied they neither adhered to the glass nor to oral mucosa, contrary to film-coated crystals alone which partly remained in the glass where they had been mixed with water, and which adhered strongly to oral mucosa.

EXAMPLE 2

Preparation of a pre-mixed gel and coating of potassium chl ride crystals with a swelling coating

5 100 g of diffusion film-coated potassium chloride crystals which were prepared as described above were coated with a coating mixture composed of 4.5 g of HPMC 50 AB, 1.5 g of PEG 6000, 2.0 g of propylene glycol, 6.0 g of Polyplasdone XL and 300 g of purified water. The coating mixture was prepared by grinding the Polyplasdone carefully
10 in a mortar followed by addition of the other solids to the mortar. The solids mixture was mixed with water at room temperature by dispersion for 2 x 10 min. at about 6000 rpm on a Silverson Laboratory mixer emulsifier model L2 air provided with a high shear screen and downthrust propeller. The propylene glycol was added during the final
15 dispersion. The coating mixture was sieved through a 0.35 mm mesh sieve.

Coating of the film-coated potassium chloride crystals was carried out in a fluid bed (which had been pre-heated for 5 min.) in a manner known per se at a rate of 2.0 g of the coating mixture/min., an inlet air temperature of 43-48°C and an outlet air temperature of 34-40°C.
20 The coated crystals were dried for 5 min. at 50°C. The entire coating procedure took 180 min. The resulting crystals had a white, slightly matt surface which under the microscope (magnification x 63) was observed to be porous and blistered.
25

A ready-to-use composition may be prepared by mixing 2.13 g of the potassium chloride crystals coated with a swelling coating with 21.07 g of a pre-mixed gel prepared as described in Example 1 for 5-10 seconds to produce a uniform distribution of the coated crystals in the viscous gel. When the composition was allowed to stand for 1-2 min., a highly viscous gel of the swollen coating and the gel could be observed. On further stirring the gel became more viscous, and the diffusion film-coated potassium chloride crystals could be observed in the gel. When the viscous composition was carefully placed on a flat support and rinsed with water, the viscous medium could be separated from the coated crystals which were found to be surrounded by the gel. It was observed under the microscope (magnification x 40)

that the crystals were surrounded by a 1/2-2 mm thick highly viscous gel.

This formulation made the crystals easy to swallow, and when a glass
5 in which the composition had been poured was emptied they neither adhered to the glass nor to oral mucosa, contrary to film-coated crystals alone which partly remained in the glass where they had been mixed with water, and which adhered strongly to oral mucosa.

10 EXAMPLE 3

Preparation of a powder composition containing sodium alginate and sucrose crystals coated with a calcium phosphate-containing coating

15 100 g of diffusion film-coated sucrose crystals prepared as described in Materials and Methods were coated with a coating mixture composed of 3.0 g of HPMC 50 AB, 1.0 g of propylene glycol, 2.4 g of calcium hydrogen phosphate, 0.8 g of PEG 6000 and 100 g of purified water.

20 The coating mixture was prepared by thoroughly grinding the HPMC and the calcium hydrogen phosphate in a mortar. Purified water was slowly added with vigorous stirring with a beater. Finally, PEG 6000 and propylene glycol were added with continued stirring for about 5 min. The coating mixture was sieved through a 0.35 mm mesh sieve.

25 The coating of the crystals was performed in a fluid bed (which had been pre-heated for 10 min.) in a manner known per se, at a rate of 3.5 g of the coating mixture/min., at inlet air temperature of 45-47°C and an outlet air temperature of 33-36°C. The coated crystals were dried at the same temperature for 5 min. The entire coating procedure took 50 min. The resulting crystals had a white, slightly matt surface which under the microscope (magnification x 63) was observed to be highly porous.

30 A powder component containing sodium alginate was prepared from 12.0 g of SOBALG FD 167, 6.0 g of SOBALG FD 170, 7.0 g of sodium hydrogen carbonate, 12.5 g of tartaric acid and 57.5 g of dextrose. These ingredients were thoroughly ground in a mortar.

Unit dosages of the dry composition were prepared by filling 0.72 g of this powder component and 1.0 g of the coated sucrose crystals into sachets No. 6.

5 A ready-to-use composition was prepared by adding the contents of a sachet to about 20 ml of purified water and stirring with a spoon for about 30 seconds. The mixture was allowed to stand for about 2 min. at room temperature followed by careful stirring for about 5 seconds to obtain a uniform distribution of the crystals in the resulting viscous medium.

10

When the viscous composition was carefully placed on a flat support and rinsed with water, the viscous medium could be separated from the crystals which were found to be surrounded by a cohesive sol. Under the microscope (magnification x 40) the crystals were observed to be 15 surrounded by a 1/2-2 mm thick clear sol.

This formulation made the crystals easy to swallow, and when a glass in which the composition had been poured was emptied they neither adhered to the glass nor to oral mucosa, contrary to film-coated 20 crystals alone which partly remained in the glass where they had been mixed with water, and which adhered strongly to oral mucosa.

EXAMPLE 4

25 Preparation of a powder composition containing sodium alginate and acetylsalicylic acid crystals coated with a swelling calcium hydrogen phosphate-containing coating

30 100 g of acetylsalicylic acid crystals were coated with a coating mixture composed of 1.5 g of HPMC 15, 1.5 g of HPMC 50 AB, 1.0 g of propylene glycol, 0.8 g of PEG 6000, 2.4 g of calcium hydrogen phosphate, 2.0 g of Avicel® PH 101 and 100 g of purified water.

35 The coating mixture was prepared by slowly adding purified water to the two HPMC grades with vigorous stirring with a beater. Avicel® PH and PEG 6000 were added with continued stirring for 5 min. after

which the suspension was dispersed as described in Example 2. Propylene glycol and calcium hydrogen phosphate were added with continued dispersion for 1 min. as described in Example 2. The coating mixture was sieved through a 0.35 mm mesh sieve.

5 The coating of the crystals was performed in a fluid bed (which had been pre-heated for 10 min.) in a manner known per se, at a rate of 3.5 g of the coating mixture/min., an inlet air temperature of 44-45°C and an outlet air temperature of 35-36°C. The coated crystals
10 were dried for 5 min. The crystals were then sieved through a 0.5 mm mesh sieve. The resulting crystals had a white, matt surface which under the microscope (magnification x 63) was observed to be grainy and porous. Furthermore, the crystals had formed small agglomerates.

15 The coated crystals were mixed with a powder component containing sodium alginate prepared as described in Example 3 at the dosage level indicated in Example 3.

20 A ready-to-use composition was prepared from the dry mixture as described in Example 3 with the exception that the composition was stirred for 1 minute and allowed to stand at room temperature for about 30 seconds.

25 When the viscous composition was placed on a flat support and rinsed with water, the viscous medium could be separated from the crystals which were found to be surrounded by a cohesive sol. Under the microscope (magnification x 40) the crystals were observed to be surrounded by a 1/2-2 mm thick clear sol.

30 This formulation made the crystals easy to swallow, and when a glass in which the composition had been poured was emptied they neither adhered to the glass nor to oral mucosa, contrary to film-coated crystals alone which partly remained in the glass where they had been mixed with water, and which adhered strongly to oral mucosa.

EXAMPLE 5

Preparation of a tablet composition containing sodium alginate, alginic acid and potassium chloride crystals coated with a calcium sulphate-containing film

5

100 g KCl crystals were coated with 86.7 g of a diffusion film coating suspension containing 0.56 g of HPMC 5, 0.12 g of magnesium stearate, 1.05 g of talc, 47.47 g of purified water and 37.5 g of Eudragit® NE 30D. The film coating suspension was prepared and coated
10 on the crystals according to the method disclosed in the European published specification No. 153 105.

The resulting coated crystals were then coated with 20 g of a coating suspension containing 13.04 g of purified water, 2.5 g of calcium sulphate, 0.20 g of PVP, 0.01 g of antifoam emulsion, 0.03 g of polysorbate 20 and 4.22 g of Eudragit® NE 30 D.
15

The film coating suspension was prepared by dispersing (vide Example 2) calcium sulphate and PVP in purified water at a temperature of about 60°C. After cooling, the dispersion was continued for a further 20 10 minutes. The remaining ingredients were admixed with continuous stirring on a magnetic stirrer (Struer type M 21) set at speed 3.

The crystals were coated and hardened according to the method disclosed in European published specification No. 153 105 and Example 4.
25

30 The coated crystals were sieved to a fraction of 0.41-1.18 mm. The resulting crystals had a pale grey, matt surface which under the microscope (magnification x 63) was observed to be slightly grainy, but otherwise clear and translucent.

A granulate was prepared from 3.2 g of sodium bicarbonate and 20 g of SORALG FD 160. 21 g of liquid composed of 0.6 g PVP dissolved in 16.2 g purified water and 4.2 g of isopropanol was used as the granulation liquid. The moistened components were sieved (0.71 mm) and dried at 40°C for 3 hours. The granulate was sieved (0.71 mm) before use.
35

A powder component composed of 2.0 g of citric acid (as the powdered monohydrate thereof), 14.0 g sieved (0.3 mm) of titanium dioxide,

2.0 g of SOBALG PH 060, 0.6 g of colloidal silica, 1.6 g of powdered saccharine sodium and 56.0 g of Avicel® PH 101 were mixed for 10 minutes in a small cube mixer (Erweka type AR 400, 3.5 liter).

5 The powder, granulate and 100 g of coated crystals were mixed for 5 minutes in a cube mixer. The mixture was compressed into capsule-shaped tablets (breaking strength: about 130 N, gross weight: 2.00 g) in an eccentric press (Diaf type TM-20). A ready-to-use composition was prepared by stirring one tablet in 20 ml of cold (about 13°C) tap water by means of a spoon. The composition was stirred for about 70
10 seconds resulting in the formation of a viscous medium. When the viscous composition was placed on a flat support and rinsed carefully with water, the viscous medium could be separated from the coated crystals which were found to be surrounded a white, cohesive sol. No residues of a tablet core were observed. Under the microscope (magnification x 40) it was observed that the crystals were surrounded by
15 15 a 1/2 - 2 mm thick, white sol.

20 This formulation made the crystals easy to swallow, and when a glass in which the composition had been poured was emptied they neither adhered to the glass nor to oral mucosa, contrary to film-coated crystals alone which partly remained in the glass where they had been mixed with water, and which adhered strongly to oral mucosa.

25 EXAMPLE 6

Preparation of a powder composition, calcium sulphate-coated sucrose crystals and calcium sulphate-coated placebo microcapsules

30 250 g of placebo microcapsules were prepared by extrusion (0.8 mm, Nica model 605-14) and spheronization for 30 sec. at 800 rpm (diameter of bottom plate: 25 cm) in accordance with conventional methods. The microcapsules were composed of 50 g Avicel® PH 101 and 200 g of lactose. The powders were mixed and moistened with 70 g of purified water in a Kenwood mixer. The microcapsules were dried at
35 40°C in a drying cupboard for 4 hours and sieved (0.41-1.18 mm).

100 g of sucros crystals which had been diffusion film coated as described in Materials and Methods and 100 g of placebo micro capsules, respectively, were coated with a calcium sulphate-containing coating suspension as described in Example 5 and sieved (0.425-3.0 mm and 0.425-1.18 mm, respectively).

A powder component composed of 90 g SOBALG FD 160, 34.5 g of tartaric acid, 59.9 g of rice starch, 71.8 g of sieved (0.3 mm) titanium dioxide, 8.2 g of sodium citrate, 28.0 g of sodium bicarbonate, 6.0 g PEG 6000 and 2.0 g of saccharine sodium was prepared as follows: Rice starch, titanium dioxide, sodium citrate, sodium bicarbonate, PEG 6000 and saccharine sodium were ground in a Fritsch Pulverisette model 14 (0.2 mm screen and high speed). The resulting powder was mixed with SOBALG FD 160 and tartaric acid for 10 minutes in a small cube mixer as described in Example 5.

The sucrose crystals and placebo microcapsules and powder component were stored in separate containers before use.

1.5 ml of powder, 1.0 ml of coated sucrose crystals and 1.0 ml of 20 coated placebo microcapsules were added to a small beaker (max 5 ml). The 3 components were transferred to a 100 ml beaker. A ready-for-use composition was prepared by adding 30 ml of cold tap water and stirring with a spoon for about 60 sec. The resulting viscous composition was immediately placed on a flat support and rinsed carefully with water, whereby the viscous medium was separated from the crystals and microcapsules which were found to be surrounded by a white, cohesive sol. Under the microscope (magnification x 40) it was observed that the crystals and microcapsules were surrounded by a 1/2 - 2 mm thick white sol.

30 This formulation made the crystals easy to swallow and when a glass in which the composition had been poured was emptied they neither adhered to the glass nor to oral mucosa, contrary to film-coated crystals alone which partly remained in the glass where they had been mixed with water and which adhered strongly to oral mucosa.

Furtherm re, 1.5 ml of the powder component and 2.5 ml of the coated microcapsules were stirred in 30 ml of cold tap water for about 60 sec., whereby similar r sults wer btain d as described above.

5

10

15

20

25

30

35

CLAIMS

1. An oral composition which is adapted to be dispersed in an aqueous carrier substantially immediately prior to administration and which
5 comprises a multiplicity of particles comprising an active substance, said particles being combined with one or more gelling or swelling agents capable of forming a viscous medium around the particles in an aqueous carrier as well as being provided with a masking surface layer when dispersed in the aqueous carrier.
- 10 2. A composition according to claim 1, wherein the masking surface layer is provided by an increased viscosity of the viscous medium in the immediate vicinity of the particles, relative to the viscosity of the surrounding aqueous carrier.
- 15 3. A composition according to claim 1, wherein the particles are admixed with the gelling or swelling agent or agents.
4. A composition according to claim 1, wherein the particles are granulated together with the gelling or swelling agent or agents.
20 5. A composition according to claim 1, wherein the particles are coated with a coating which is composed of at least one layer comprising the gelling or swelling agent.
- 25 6. A composition according to claim 1, wherein the particles have a size in the range of about 0.05-7 mm.
7. A composition according to claim 1 which comprises two or more active substances.
- 30 8. A composition according to any of claims 1-7, wherein the active substance is selected from drugs, vitamins, micronutrients and macronutrients.
- 35 9. A composition according to any of claims 1-8, which further comprises a substance increasing the viscosity of the viscous medium formed around the particles by the gelling or swelling agent in an aqueous carrier.

10. A composition according to claim 9, wherein the viscosity-increasing substance is incorporated in the particles.
- 5 11. A composition according to claim 9, wherein the viscosity-increasing substance is incorporated in a coating provided on the particles.
12. A composition according to any of claims 1-11 which is in unit dosage form.
- 10 13. A composition according to claim 12 which is in the form of a sachet, capsule or tablet.
14. A composition according to claim 11 which comprises at least 200 mg of the active substance.
- 15 15. A method of preparing a ready-to-use composition which comprises a multiplicity of particles comprising an active substance, the particles being combined with a gelling or swelling agent, the method comprising mixing said particles combined with said gelling or swelling agent with an aqueous carrier substantially immediately prior to administration thereof to form a viscous medium of the gelling or swelling agent around the particles and to provide a masking surface layer on the particles.
- 20 16. A method according to claim 15, wherein the masking surface layer is provided by an increased viscosity of the viscous medium in the immediate vicinity of the particles relative to the viscosity of the surrounding aqueous carrier.
- 25 17. A method of preparing a ready-to-use composition which comprises a multiplicity of particles comprising an active substance, the method comprising adding a gelling or swelling agent to an aqueous carrier to form a viscous medium and mixing said particles with the viscous medium substantially immediately prior to administration of the composition to form a viscous medium of the gelling or swelling agent around the particles and to provide a masking surface layer on the particles.
- 30
- 35

18. A method according to claim 17, wherein the masking surface layer is provided by an increased viscosity of the viscous medium in the immediate vicinity of the particles relative to the viscosity of the surrounding aqueous carrier.

5

19. A ready-to-use composition as prepared by the method of claim 15 or 17.

10

20. A composition according to claim 19, wherein the viscous medium shows an increased viscosity in the immediate vicinity of the particles relative to the viscosity of the surrounding aqueous carrier.

21. A composition according to claim 19 or 20, wherein the particles are coated with a coating which is composed of at least one layer comprising the gelling or swelling agent.

15

22. A composition according to any of claims 19-21, wherein the particles or coating further comprises a substance increasing the viscosity of the viscous medium around the particles.

20

25

30

35

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK88/00044

I. CLASSIFICATION & SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 61 K 47/00, 9/14, 9/16

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System	Classification Symbols
IPC 4	A 61 K
US C1	424:31-35

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT*

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. 13
X	EP, A., 0 084 190 (FISONS PLC) 27 July 1983 see examples & BE, 895259 FR, 2517543 LU, 84509 JP, 58113188	1, 3, 8, 15
X	EP, A., 0 207 032 (LEJUS MEDICAL AKTIEBOLAG) 30 December 1986 see claims, examples, column 3, lines 1-6	1, 3, 8, 15
X	SE, B., 431 937 (PERSTORP AB) 12 March 1984 see claims, examples & GB, 2041958 DE, 3003107 SE, 7900738	1, 3, 8, 15
X	FR, A1, 2 473 307 (GRIMBERG S G, CHANCOGNE G P, BLANIE J M) 17 July 1981 see claims	1, 3, 8, 15 .../...

- * Special categories of cited documents: *
 "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "G" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

1988-06-06

Date of Mailing of this International Search Report

1988-06-10

International Searching Authority

Swedish Patent Office

Signature of Authorized Officer

Agneta Tannerfeldt
Agneta Tannerfeldt

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	EP, A., O 136 013 (UNITIKA LTD.) 3 April 1985 see examples & JP, 60036410 US, 4704268	17
X	EP, A., O 190 826 (WARNER-LAMBERT COMPANY) 13 August 1986 see examples & JP, 61204119	1, 3, 8, 15